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Solving Various STR Structures of Dystrophin Protein

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Muscular dystrophy is a debilitating disease that varies in severity but is the result of either the complete absence of or a modified malfunctioning form of the dystrophin protein. Dystrophin is a rod-shaped protein consisting of amino- and carboxy- terminal binding domains linked by a central rod composed of 24 copies of a spectrin-type repeat (STR) motif and four non-homologous regions termed hinges. Historically it has been thought that STRs are repeating and homologous. However, recent work has shown that various STRs exhibit markedly different stabilities, and that some regions appear disordered and flexible and suggest that STRs may function as hinge-like regions. We have obtained protein crystals of the d5 and d16–17 STR's from the human dystrophin protein and collected < 2-Å resolution data at SER-CAT. Molecular replacement methods have proven unsuccessful to date as a suitable model remains elusive. Multiple isomorphous replacement with heavy atoms has also proven fruitless as the soaked P1 crystals have lacked the redundancy and isomorphism required for single-wavelength anomalous dispersion and multiwavelength anomalous diffraction phasing. Alternative approaches are currently underway to overcome these obstacles and produce the first high-resolution STR structure and glean direct evidence as to the role of these STRs.